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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,951	08/20/2001	Nobuhiro Sato	213126US0X	4655

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application N .	Applicant(s)	
	09/931,951	SATO ET AL.	
	Examin r	Art Unit	
	Vanessa L. Ford	1645	

--Th MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

THE REPLY FILED 13 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *13 June 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see Advisory Attachment*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *16-18*.

Claim(s) withdrawn from consideration: *1-13 and 15*.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *Advisory Attachment*

Advisory Action Attachment

1. Applicant's response filed June 13, 2003 is acknowledged. Applicant's amendment, response and submission of the Ohkusa et al reference are acknowledged. Claim 16 has been amended.

2. For clarification of the record, the rejection under 112, first paragraph in the Final Office action (mailed January 13, 2003) was maintained for claims 16-18 and not claim 14 which was previously cancelled as indicated in the body of the 112, first paragraph rejection. It should be noted that the rejection of claim 14 under 35 U.S.C.102(b) anticipated by Danielsson et al and the objection to the specification were withdrawn in the Final Office action prior to the interview with Applicant on April 15, 2003.

3. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Maintained

4. The rejection under 35 U.S.C. 112, second paragraph is maintained for newly presented claims 16-18 for the reasons set forth on pages 2-3, paragraph 4 of the previous Office Action.

The rejection was on the grounds that the claims rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: 1) providing a sample (i.e. sample source, 2) determining that the target antibody (i.e. *Fusobacterium varium*) is obtained and not antibodies to a mixture of colonic bacteria,

3) determining the amount of antibody significant to make a diagnosis and 4) the correlation as to how to a diagnose of ulcerative colitis is made using the antibody.

Applicant urges that the 35. U.S.C. 112, second paragraph rejection is obviated by the amendment. Applicant urges that claim 14 has been cancelled and rewritten as claims 16-18 to insert method steps.

Applicant urges that claim 16 has been amended to recite the necessary correlation and diagnosis step. Applicant urges that the alleged omitted steps are inherently embraced by the claims as presented. Applicant urges that the skilled artisan would readily appropriate preparation steps and detection limits associated with Western blotting and/or ELISA methods.

Applicant's arguments filed June 13, 2003 have been fully considered but they are not persuasive. The claims are incomplete for omitting essential steps. For example, how were the ELISA and Western blotting methods used, were whole *Fusobacterium varium* organisms used to detect antibodies or were proteins of *F. varium* (antigens) used in the assays? It is the Examiner's position that claims 16-18 are indefinite and do not meet the requirement of 35 U.S.C. 112, second paragraph.

5. The rejection of claims 16-18 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 3-7, paragraph 5 of the previous Office Action.

The rejection was on the grounds that claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 16-18 are drawn to a method of diagnosis of ulcerative colitis.

The specification is only enabled for a method of detecting *Fusobacterium varium* antibodies and not a method of diagnosis of ulcerative colitis.

There are several factors that contribute to the diagnosis of a disease or disorder that are well known in the art. These factors include: 1) the known etiologic agent that causes the disease, 2) the cross reactivity of multiple microorganisms involved in the disease and 3) the immunopathogenesis associated with the disease. The etiologic agent associated with ulcerative colitis is unknown. This is evidenced by Sartor *(Gasreoenterology Clinic of North America (UNITED STATES), September 1995, 24, p. 475-507).* Sartor teaches that ulcerative colitis and Crohn's disease collectively are referred to as inflammatory bowel disease (IBD), are chronic, spontaneously relapsing disorders of unknown cause (see the Abstract). Braegger *(Acta Paediatr Suppl. 395 : 18021, 1994)* teaches that the etiology and pathogenesis of chronic inflammatory bowel disease are unknown (see the Abstract). Fox et al *(Infection and Immunity, April 1999, p. 1757-1762)* suggest that *Helicobacter* species are associated with colitis (the Abstract). It is unpredictable as to which microorganisms may be involved in ulcerative colitis. This is evidenced by Macpherson et al *(Gut, 1996,38:365-375).* Macpherson et al suggest that there may be multiple organisms involved in inflammatory bowel disease. Macpherson et al disclose experiments that show that in relapse of inflammatory bowel disease there is a breakdown of tolerance to the normal commensal flora of the gut (which includes multiple organisms). Multiple microorganisms that reside in the gastrointestinal tract are evidenced by Coleman et al, *(Applied and Environmental Microbiology, October 1996, p. 3632-3639).* Coleman et al teach that there are six microbial competitors in the human gastrointestinal tract and they are *Escherichia coli, Enterobacter aergenes, Bacteroides ovatus, Fusobacterium varium* and *Enterococcus faecalis.* Cross-reactivity is a factor to be considered since there are multiple microorganisms that reside in the gastrointestinal tract. Marx et al *(Infection and Immunity, June 1982, 36 (3) p. 943-948)* teach that cross-reactivity exist between species of the genera *Bacteroides* and species of the genera *Fusobacterium* (see the Abstract). Ushijima et al *(Journal of Medical Microbiology, September 1990, 33 (10:17-22)* further teach that cross-reactivity exists between species of colonic bacteria (see the Abstract). Immunopathogenesis is also associated with ulcerative colitis. Braegger *(Acta Paediatr Suppl. 395 : 18021, 1994)* teaches that immunological mechanisms may play a significant role in mediating the intestinal lesion and some of the systemic manifestations of Crohn's disease and ulcerative colitis. Braegger teaches that Crohn's disease and ulcerative colitis present dense infiltration of inflammatory cells, increased plasma cells, T lymphocytes, macrophages and neutrophils (page 18, 1st column). Braegger further teaches that ulcerative colitis may be caused by an IgG-mediated autoimmune process to the colon mucosa (pages 20-21).

Since the detection of antibodies is used in the claimed invention to diagnose ulcerative colitis, one skilled in the art would have to possess the knowledge or be provided with sufficient guidance with regard as to how to detect only the target microorganism (i.e. *Fusobacterium varium*) and not a mixture of colonic bacteria antibodies in order to make a diagnosis of ulcerative colitis. The cited references have shown that unpredictability and uncertainty exists regarding which microorganism or microorganisms are the causative agents of ulcerative colitis. Other references have been cited that show that there are multiple microorganisms that reside in the

gastrointestinal tract and references have also been cited to show the immunopathogenesis associated with the disease. Therefore, it can be concluded that undue experimentation would be required to use the claimed method of diagnosing ulcerative colitis without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

The specification fails to teach how a sample is obtained? How to determine the amount of antibody significant to make a diagnosis of ulcerative colitis? How to assure that the target antibody (i.e. *Fusobacterium varium*) is obtained and not a mixture of antibodies from other colonic bacteria? Nor does the specification provide a correlation between how to diagnosis of ulcerative colitis and the detection of *Fusobacterium varium* antibodies. Therefore, it is unclear as to how to make a diagnosis of ulcerative colitis using the claimed method.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification as to the etiologic agent that causes ulcerative colitis 3) there are limited working examples which suggest the detection of *Fusobacterium varium* antibodies 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability regarding the cross reactivity of microorganisms that inhabit the gastrointestinal tract and uncertainty of the etiologic agent of ulcerative colitis in the art, it is determined that it would require undue experimentation to use the claimed invention.

Applicant urges that the claim 16 has been amended to specifically indicate that the classification of ulcerative colitis sought to be diagnosed is "ulcerative colitis caused by *Fusobacterium varium*. Applicant urges that arguments regarding mixtures of antibodies from other colonic bacteria are moot in view of the newly amended claims. Applicant urges that those skilled in the art could easily carry out the method of claim 16

by using either a western blotting method or an enzyme-linked immunosorbent assay (ELISA). Applicant urges that Example 1 of the specification discloses that *Fusobacterium* can be isolated and an antibody specific thereto can be obtained. Applicant urges that the Ohkusa et al reference has established a clear indication of a causal relationship between *Fusobacterium varium* and ulcerative colitis. Applicant urges that Ohkusa et al demonstrate that only sera from patients with ulcerative colitis gave specific reactions with *Fusobacterium varium* in Western blot assays from a collection of patients suffering from active ulcerative colitis, Crohn's disease, ischemic colitis and colon adenomas. Applicant urges that strong signals were evident at 70 and 48 kDa with sera from 61% of the patients with active UC, 13% with Crohn's disease and 29% of the healthy controls and only antigen from *Fusobacterium varium* gave specific bands of reactivity. Ohkusa et al demonstrate that *Fusobacterium varium* was detected immunohistochemically in the exudates, surface mucus and crypts of the colonic mucosa in 84% of patients with active UC and in contrast only 13% of the patients in remission from UC, 16% of patients with Crohn's disease, 13% of patients with ischemic colitis and 3% of patients with colon adenoma gave positive immunostaining reactions. Applicant urges that the present invention is enabled as defined by 35 U.S.C. 112, first paragraph.

Applicant's arguments filed June 13, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention. The prior art cited above and Ohkusa et al

agree that the etiology of ulcerative colitis is unknown but the disease shares histological features with colitis caused by infectious agents (page 849). Ohkusa et al teach that *Fusobacterium varium* antibodies where detected in 61% of patients with active UC opposed to 13% of patients with Crohn's disease and 29% of the healthy control patients (page 850). Ohkusa et al teach that the detection of serum antibodies to *F. varium* has the potential to become a differential diagnosis marker in inflammatory bowel disease (page 852). The specification teaches that "in an ELISA and immunohistochemistry with *F. varium* proteins an (as) antigen, mean optical density and the detection rate were higher for our patients than for subjects with Crohn's disease or other controls" (page 8, Example 1). One of skill in the art cannot conclude that the detection of *Fusobacterium varium* is a diagnostic maker for ulcerative colitis since antibodies of *Fusobacterium varium* were detected in other inflammatory bowel disease and as well as in healthy individuals (controls). Coleman et al, *(Applied and Environmental Microbiology, October 1996, p. 3632-3639)* teach that *F. varium* are among six microbial competitors that reside in the human gastrointestinal tract. One of skill in the art would expect that *Fusobacterium varium* would be detected in healthy individuals as well as individuals suffering from an inflammatory bowel diseases. Ohkusa et al may have established that there appears to be a relationship between *F. varium* and ulcerative colitis since a high number of *F. varium* antibodies were detected in UC patients. However, Ohkusa et al have not established that *Fusobacterium varium* is the causative agent of ulcerative colitis nor has the instant specification established that *Fusobacterium varium* is the causative agent of ulcerative colitis. The instant

specification is not enabled for a method for making a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient since the causative agent of UC remains unknown. The specification has failed to provide the guidance needed for the skilled artisan to use the claimed method in a manner that is commensurate with the claims. Therefore, it can be concluded that undue experimentation would be required to use the claimed method of diagnosing ulcerative colitis caused by *Fusobacterium varium* without proper guidance.

Status of Claims

6. No claims allowed.

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
July 28, 2003

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